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CASE REPORT

Acute coronary syndrome associated with essential thrombocythemia

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Summary Although essential thrombocythemia (ET) has been rarely reported to cause coronary thrombosis, its appropriate management is still undefined. We describe a case of acute coronary syndrome in a patient with ET. A 47-year-old woman with ET complained of severe acute chest pain. Primary coronary angiography showed severe stenosis with thrombus in the proximal left anterior descending coronary artery. The patient was treated with anti-platelet drugs and hydroxyurea to prevent in-stent thrombosis, and subsequently underwent successful coronary angioplasty using aspiration and a distal protection device without thrombotic coronary complications.

Introduction

Essential thrombocythemia (ET), a clonal myeloproliferative disorder, increases the risk of both thrombosis and hemorrhage. Recent studies have shown that thrombotic complications, especially thrombus in the cerebral, coronary, and peripheral arteries, were more frequent than hemorrhage in patients with ET, and the incidence of acute coronary disease in patients with ET was 9.4% [1].

Several drugs are presently available for the prevention of thrombus. Aspirin reduces coronary thrombosis in patients with an elevated platelet count and cardiovascular risk factors [2]. Hydroxyurea is effective for preventing thrombus in patients with ET who are at high risk for thrombotic complications. The distal embolization of atherothrombotic material often occurs during percutaneous coronary intervention (PCI) in patients with thrombotic lesions, and its occurrence is associated with worse long-term outcomes [3]. The use of both aspiration thrombectomy and distal protection for thrombotic lesions gives excellent angiographic results.

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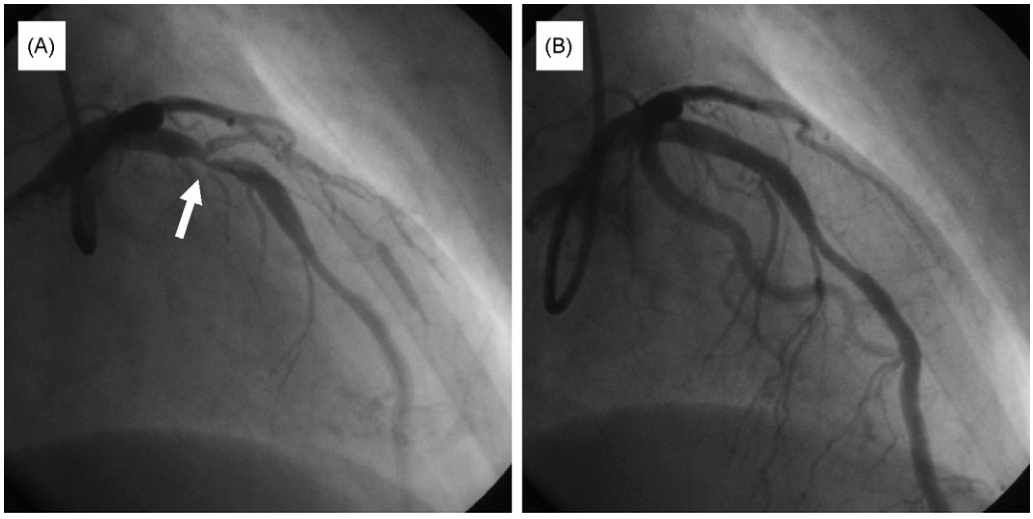

Figure 1 Left coronary angiography (right anterior oblique cranial). (A) Severe stenosis with thrombus of the left anterior descending coronary artery. (B) Successful angioplasty using aspiration thrombectomy, distal protection, and a bare-metal stent without distal embolization.

Since there is as yet no standard treatment for acute coronary syndrome (ACS) with ET, we describe successful PCI using both aspiration thrombectomy and distal protection in combination with platelet-lowering therapy in a patient with ACS caused by ET.

Case report

A 47-year-old woman with recently diagnosed ET was brought to our hospital because of severe chest and back pain lasting for 30 min. She was diagnosed with ET based on bone marrow histology. Her platelet count was 1,295,000/mm^3. She was a smoker and had a past history of hypertension five years previously, but had no history of hyperlipidemia, diabetes, or hemorrhagic disorder. The electrocardiogram on admission showed ST depression in leads V_3–V_6, and the echocardiogram showed a slight reduction in wall motion in the antero-septal region, consistent with ACS. Therefore, anti-platelet therapy with oral aspirin (100 mg/day) and clopidogrel (75 mg/day) was initiated. Diagnostic coronary angiography revealed severe stenosis with thrombolysis in myocardial infarction (TIMI) grade II in the proximal left anterior descending (LAD) coronary artery with thrombus (Fig. 1). However, thrombotic complications after PCI, such as subacute thrombosis, were more likely because of the presence of ET, and thus platelet-lowering therapy using hydroxyurea (1000 mg/day) was initiated. Heparin (10,000 U/day) was administered to prevent new thrombus in addition to oral anti-platelet therapy until PCI. Two weeks after the initiation of

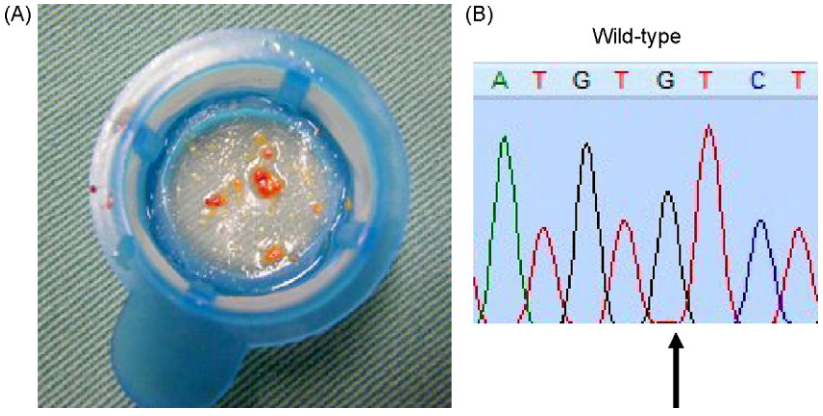

Figure 2 (A) The red and white thrombotic materials retrieved by Thrombuster III. (B) Sequence traces showing a wild-type sequence in JAK2. Mutation screening was performed as described previously [14].

Figure 3 Total occlusion of the right brachial artery six months after percutaneous coronary intervention.

hydroxyurea, the platelet count was decreased to 839,000/mm^3, and PCI was performed. Thrombectomy using an aspiration device (Thrombuster III, Kaneka Corp., Osaka, Japan) was attempted with distal protection (Filtrap, Nipro, Osaka, Japan). The red and white thrombus retrieved by the Thrombuster III was confirmed (Fig. 2A). A 4.0 mm $\times$ 16 mm bare-metal stent (Liberte, Boston Scientific Japan, Tokyo, Japan) was implanted to the LAD, resulting in removal of the thrombus without no reflow phenomenon along with successful angioplasty. Although six-month follow-up coronary angiography revealed no restenosis, late lumen loss as assessed by quantitative coronary angiography was 1.35 [average = 0.69 $\pm$ 0.58 (mean $\pm$ S.D.), unpublished data]. In addition, total occlusion with thrombus was seen in the right brachial artery (Fig. 3), and asymmetry of the brachial pulses and blood pressure was found. Anticoagulation therapy with warfarin was started in addition to anti-platelet therapy and hydroxyurea to prevent further thrombotic complications. Since a single point mutation (V617F) has frequently been identified in janus kinase 2 (JAK2) in patients with ET [4], we analyzed this mutation, but this patient had wild-type JAK2 (Fig. 2B).

Discussion

ET is a myeloproliferative disorder characterized by the monoclonal proliferation of hematopoietic stem cells. ET is manifested clinically by the overproduction of platelets in the absence of a definite cause and leads to thrombus formation in systemic arteries including the coronary artery. The overall rates of thrombosis and hemorrhage at diagnosis during follow-up have ranged from 7% to 17% and 8% to 14%, respectively [5].

Age, previous thrombotic events, and a long duration of thrombocytosis have been identified as major risk factors for thrombosis in previous reports [6]. Age over 60 and a history of major ischemic events were also risk factors for atherothrombotic complications in a large study of 148 ET patients [7]. Among cardiovascular risk

factors, hypertension, hypercholesterolemia, and smoking were also associated with an increased risk of developing major vascular complications in some studies [6]. In this case, a history of angina, hypertension, and smoking were included as risk factors for thrombotic events. In addition to ischemic events, thrombotic occlusion in the right brachial artery was noted. A previous study showed that a history of thrombosis at diagnosis was significantly associated with recurrent thrombosis [8]. In addition, another thrombotic event occurred repeatedly despite treatment with anti-platelet drugs and hydroxyurea. However, we cannot exclude the possibility that it might be induced by some injury sustained during the cardiac catheterization procedure, which was performed by the right radial artery approach.

Platelet-lowering therapy with hydroxyurea was started because this case was classified as high risk for thrombotic complications. Hydroxyurea has emerged as the treatment of choice for high-risk patients with ET because of its efficacy and the rarity of acute toxicities. A randomized clinical trial demonstrated that there were significantly fewer thrombotic complications in a hydroxyurea-treated group than in a control group (1.6% vs 10.7%, $p = 0.003$) [9]. However, in our patient, a new thrombotic event occurred in the right brachial artery despite treatment with hydroxyurea. Cortelazzo et al. showed that ET patients with platelet counts below 600,000/mm^3 have a reduced rate of thrombosis [6]. In this case, platelet counts decreased from 1,295,000/mm^3 to 839,000/mm^3 after treatment with hydroxyurea. Our platelet-lowering therapy with hydroxyurea might have been inadequate to prevent thrombosis. Consensus-based practice guidelines for the treatment of ET have recently been developed in Italy [5]. Young (age <60 years) asymptomatic patients with platelet counts below 1,500,000/mm^3 are at lower risk for thrombosis and can be followed without treatment. For high-risk patients (history of thrombosis, hemorrhagic complications, platelet count >1,500,000/mm^3, or age >60 years), hydroxyurea is the treatment of choice because it has been shown to be effective at preventing thrombotic complications in a randomized clinical trial. However, the possible long-term leukemogenicity of this drug remains a major concern. Anagrelide and interferon-α could overcome this concern and should be considered for high-risk younger patients. Our case was a high-risk patient because of a history of thrombosis, and therefore we chose hydroxyurea for platelet-lowering therapy.

The combination of aspirin with clopidogrel and warfarin in addition to hydroxyurea has been administered for the prevention of recurrent thrombosis. De Stefano et al. [10] demonstrated that long-term treatments with anti-platelet or anticoagulant agents were independently effective for preventing recurrence, with reductions of re-thrombosis of 58% and 68%, respectively. Furthermore, in a review by Landolfi and Di Gennaro [11], they considered that more aggressive anti-platelet therapy with the combination of aspirin and clopidogrel in patients with prior ACS might be beneficial for preventing re-thrombosis. However, anti-platelet therapy plus anticoagulants resulted in a higher incidence of major bleeding (2.8% patient-years) compared with anti-platelet drug or anticoagulants alone (0.8% and 0.9% patient-years, respectively) [10,12]. Careful follow-up would be needed to monitor bleeding complications with multi anti-thrombotic therapy in this case.

Recently, 4 groups reported that JAK2 V617F mutation could be detected in more than 30% of patients with ET [13]. Furthermore, the Medical Research Council Primary Thrombocythemia-1 Trial studied the effect of JAK2 V617F mutation on treatment outcome in patients with ET, and demonstrated that JAK2 V617F mutation-positive patients were much more sensitive to hydroxyurea [14]. In this case, although we investigated JAK2 V617F mutation, this mutation was not identified. This may have been associated with the inadequate decrease in platelet counts despite treatment with hydroxyurea.

Intracoronary thrombus remains a challenge for interventional catheter-based techniques. Distal embolization of thrombus after balloon inflation and stent implantation carries an increased risk of a poor clinical outcome [13]. Therefore, distal embolization is considered to be a major cause of insufficient reperfusion. In this case, we used both aspiration thrombectomy and distal protection to prevent distal embolization, and successful angioplasty was achieved without complications.

To our knowledge, there have been 17 reports of acute myocardial infarction associated with ET in the literature. In 6 of these patients [15—19], no organic stenosis of the coronary artery after standard therapy for acute myocardial infarction was found by coronary angiography. Previous investigations for the pathogenesis of ACS have shown the importance of platelet thrombus formation caused by vascular endothelial damage resulting from plaque rupture [20]. Considering these cases, however, thrombus formation due to abnormal platelet counts might be the main underlying cause of ACS associated with ET. There have been few reports on the use of intravascular ultrasound or the his-

tological examination of coronary artery thrombus in patients with ACS associated with ET. Therefore, the characteristics of thrombus and the cause of occlusion are not precisely known. Further investigation is needed on this point, which could lead to a more appropriate therapy for thrombosis complicating ET.

In conclusion, we performed successful angioplasty without distal embolization or coronary thrombosis after stent implantation in a patient with ET. In young patients with ACS, further evaluation for an unusual cause is needed. Additional therapy, including anti-platelet drugs, anti-coagulant drugs, and hydroxyurea, should be started when a patient is diagnosed with ET.

References

[1] Rossi C, Randi ML, Zerbinati P, Rinaldi V, Girolami A. Acute coronary disease in essential thrombocythemia and polycythemia vera. J Intern Med 1998;244:49—53.

[2] Tanaka S, Nishigaki K, Ojio S, Okubo M, Yasuda S, Ishihara Y, Kubota T, Takasugi N, Kawamura I, Yamaki T, Ushikoshi H, Aoyama T, Kawasaki M, Takemura G, Minatoguchi S. Can negative cardiac effect of proton pump inhibitor and high-dose H2-blocker have clinical influence on patients with stable angina? J Cardiol 2008;52:39—48.

[3] Henriques JP, Zijlstra F, Ottervanger JP, de Boer MJ, van't Hof AW, Hoorntje JC, Suryapranata H. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. Eur Heart J 2002;23:1112—27.

[4] Kralovics R, Passamonti F, Buser AS, Teo SS, Tiedt R, Passweg JR, Tichelli A, Cazzola M, Skoda RC. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med 2005;352:1779—90.

[5] Barbui T, Barosi G, Grossi A, Gugliotta L, Liberato LN, Marchetti M, Mazzucconi MG, Rodeghiero F, Tura S. Practice guidelines for the therapy of essential thrombocythemia. A statement from the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation. Haematologica 2004;89:215—32.

[6] Cortelazzo S, Viero P, Finazzi G, D'Emilio A, Rodeghiero F, Barbui T. Incidence and risk factors for thrombotic complications in a historical cohort of 100 patients with essential thrombocythemia. J Clin Oncol 1990;8:556—62.

[7] Besses C, Cervantes F, Pereira A, Florensa L, Solé F, Hernández-Boluda JC, Woessner S, Sans-Sabrafen J, Rozman C, Montserrat E. Major vascular complications in essential thrombocythemia: a study of the predictive factors in a series of 148 patients. Leukemia 1999;13:150—4.

[8] Tefferi A, Fonseca R, Pereira DL, Hoagland HC. A long-term retrospective study of young women with essential thrombocythemia. Mayo Clin Proc 2001;76:22—8.

[9] Cortelazzo S, Finazzi G, Ruggeri M, Vestri O, Galli M, Rodeghiero F, Barbui T. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. N Engl J Med 1995;332:1132—6.

[10] De Stefano V, Za T, Rossi E, Vannucchi AM, Ruggeri M, Elli E, Micò C, Tieghi A, Cacciola RR, Santoro C, Gerli G, Vianelli N, Guglielmelli P, Pieri L, Scognamiglio F, et al. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. Haematologica 2008;93:372—80.

[11] Landolfi R, Di Gennaro L. Prevention of thrombosis in polycythemia vera and essential thrombocythemia. Haematologica 2008;93:331—5.

[12] Cortelazzo S, Marchetti M, Orlando E, Falanga A, Barbui T, Buchanan MR. Aspirin increases the bleeding side effects in essential thrombocythemia independent of the cyclooxygenase pathway: role of the lipoxygenase pathway. Am J Hematol 1998;57:277—82.

[13] James C, Ugo V, Le Couédic JP, Staerk J, Delhommeau F, Lacout C, Garçon L, Raslova H, Berger R, Bennaceur-Griscelli A, Villeval JL, Constantinescu SN, Casadevall N, Vainchenker W. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature 2005;434:1144—8.

[14] Campbell PJ, Scott LM, Buck G, Wheatley K, East CL, Marsden JT, Duffy A, Boyd EM, Bench AJ, Scott MA, Vassiliou GS, Milligan DW, Smith SR, Erber WN, Bareford D, et al. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet 2005;366:1945—53.

[15] Okayasu N, Murata M, Ueda A, Su KM, Sada T, Ito T, Hasegawa Y, Matsumoto S, Ito Y. Primary thrombocythemia and myocardial infarction in a 26-year-old woman with normal coronary arteriogram. Jpn Heart J 1981;22:439—45.

[16] Saffitz JE, Phillips ER, Temesy-Armos PN, Roberts WC. Thrombocytosis and fatal coronary heart disease. Am J Cardiol 1983;52:651—2.

[17] Douste-Blazy P, Taudou MJ, Delay M, Pris J, Sie P, Ribaut L, Galinier F, Bernadet P. Essential thrombocythaemia and recurrent myocardial infarction. Lancet 1984;2:992.

[18] Kaya H, Gündogdu M, Tekin SB, Akarsu E, Bozkurt E. Essential thrombocythemia and recurrent myocardial infarction. Clin Lab Haematol 2000;22:161—2.

[19] Tekin M, Gökaslan S, Diker E, Aydoğdu S. Development of acute coronary syndrome in three patients with essential thrombocythemia or polycythemia vera. Turk Kardiyol Dern Ars 2008;36:35—8.

[20] Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992;326:242—50.